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Compared to high and low cannabis use, moderate use is associated with fewer cognitive deficits in psychosis

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ABSTRACT

Literature on the relationship of cannabis use and cognition in schizophrenia provides the paradoxical view that cannabis use is sometimes linked with less severe impairment in neurocognition. This paper explored the possibility that this is a reflection of a dose related response between lifetime cannabis use and two forms of cognition, neurocognition and metacognition, in schizophrenia. It was hypothesized that three groups of patients could be differentiated, those with (1) little to no cannabis use with poor levels of cognition, (2) moderate cannabis use and relatively better levels of cognition and (3) high cannabis use with relatively poorer levels of cognition. Sixty-six adults with schizophrenia completed assessments of neurocognition, metacognition and months of lifetime cannabis use. A k-means cluster analysis yielded three distinct groups based on these assessments. The clusters included: (1) low cannabis/poor cognition ($n = 34$); (2) heavy cannabis/moderately impaired cognition ($n = 10$); and (3) moderate cannabis/higher cognition ($n = 22$). Consistent with our hypothesis, participants with high and moderate lifetime cannabis use had lesser impairment of neurocognition and metacognition compared to low lifetime cannabis use. Participants with moderate lifetime cannabis use also had lesser impairment of metacognition compared to low and heavy use. These findings suggest that a dose related relationship exists between cannabis use and cognition. Results could be due to an influence of pre-existing cognitive level on likelihood of lifetime cannabis use, or to an interaction between use and cognitive function.

1. Introduction

Cannabis use is a common comorbidity with schizophrenia (Kavanagh et al., 2002; Nesvåg et al., 2015), with approximately 64.4% of individuals with schizophrenia reporting lifetime use (Barnes et al., 2006) and 16% and 27% meeting the criteria for current and lifetime cannabis use disorder (Koskinen et al., 2010). Cannabis use has been associated with an earlier onset of schizophrenia (Galvez-Buccollini et al., 2012; Veen et al., 2004). Further, individuals who continue to use cannabis after their first episode of psychosis have a worse prognosis, with increased relapse and hospitalizations (Alvarez-Jimenez et al., 2012), even when controlling for other substances (Foti et al., 2010). Additionally, acute intoxication from Δ-9-tetrahydrocannabinol (Δ-9-THC), the psychoactive component in cannabis, has been shown to exacerbate psychotic symptoms in schizophrenia (D'Souza et al., 2005).

While cannabis use may exacerbate symptoms of schizophrenia, its impact on neurocognition, the most prominent form of cognition, is less clear. In particular, studies on the relationship of cannabis use and cognition in persons with schizophrenia present a paradox. On one hand, cannabis seems to negatively affect cognition in persons without schizophrenia. For example, acute, dose-related cognitive impairments have been observed in healthy individuals with cannabis (Pope et al., 1996; 2001; Bolla et al., 2002; Lundqvist, 2005; Solowij & Battisti, 2008; Crean, Crane & Mason, 2011), its psychoactive constituent Δ-9-THC (D'Souza et al., 2004; Ranganathan and D'souza 2006; Morrison et al., 2009), and synthetic cannabinoids (Gunderson et al., 2012). Additionally, cannabis use has been associated with long-term cognitive decline in healthy individuals (Fried et al., 2002; Meier et al., 2012). In schizophrenia, acute Δ-9-THC IV

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administration has also shown intensified cognitive dysfunction, as indexed by greater cognitive impairment in learning and memory (D'Souza et al., 2005). Additionally, schizophrenia patients displayed greater sensitivity to these cognitive impairments from Δ-9-THC compared to healthy controls.

On the other hand, lifetime cannabis use has been associated with less severe neurocognitive impairment in schizophrenia (de la Serna et al., 2010; Hanna et al., 2016; Jockers-Scherübl et al., 2007; Schnell et al., 2009; Yücel et al., 2012). Specifically, these studies suggest that persistent cannabis use prior to the age of 17 years old and before the onset of psychotic symptoms is associated with elevated cognitive performance compared to non-cannabis using peers. However, other studies have failed to find an association between cannabis use and elevated cognitive performance (Cleghorn et al., 1991; Pencer and Addington, 2003).

One possible explanation for this paradox is that moderate cannabis use modulates a pathway to psychosis which is distinct from other pathways in that it does not affect neurocognition at the trait level. In other words, perhaps moderate cannabis use increases risk for psychosis without concurrent neurocognitive deficits and hence those individuals appear to be more neurocognitively intact. Alternatively, there may be other persons who are heavy cannabis users who develop cognitive deficits similar to the deficits found in heavy using healthy controls. This would suggest a model in which there are at least three groups of persons including those with little to no cannabis use with poor levels of cognition, moderate cannabis use and relatively better levels of cognition and high cannabis use with relatively poorer levels of cognition. Support for this model (Fig. 1) comes from three primary findings in the literature. Firstly, there appears to be a consistent dose-dependent relationship between lifetime cannabis exposure and the later development of psychosis (Andréasson et al., 1987; Gage et al., 2016; Henquet et al., 2005a; Van Os et al., 2002; Zammit et al., 2002). Secondly, the cannabinoid system has been implicated in the potential disruption of cognitive processes observed in schizophrenia (Volk and Lewis, 2016). Finally, recent evidence suggests that people with schizophrenia with lifetime cannabis use demonstrate less cognitive impairments, compared to non-using peers (de la Serna et al., 2010; Hanna et al., 2016; Jockers-Scherübl et al., 2007; Schnell et al., 2009; Yücel et al., 2012). Important to note, these pathways are in regard to lifetime cannabis use, while acute and residual cannabis use would be anticipated to have differential effects on cognition and potentially psychotomimetic effects.

To test this possibility the current study sought to determine whether cluster analyses would differentiate three groups of patients with schizophrenia on the basis of lifetime cannabis use and neurocognition. We also included another form of cognition, metacognition, in our cluster analysis. While the relationship between metacognition, cannabis use and schizophrenia has not been extensively studied, metacognition appears to be an intuitively important domain of cognition that has potential impact on one's ability to achieve recovery. As neurocognition directly refers more to raw ability to focus, remember and process information, metacognition encompasses the specific ability to think about one's self, others and the ability to use this knowledge. Originally used in the education literature to describe an individual's awareness of learning style, the term metacognition has since been expanded to refer to a spectrum of mental activities. Metacognitive acts range from discrete processes, such as thinking about a thought, to more synthetic acts that require thoughts, feelings, and intentions to be integrated into complex representations that later enable individuals to recognize and respond to life challenges (Lysaker et al., 2013; Semerari et al., 2003). While metacognition partially overlaps conceptually with neurocognition, one operational difference between the two is that more synthetic forms of metacognition are assessed by analyzing discourse and not by the accuracy of a response to a task. Decrements in metacognition have been broadly observed in schizophrenia and contribute to functional impairment and decreased quality of life, independent of neurocognition (Lysaker et al., 2014). Previous studies have linked different forms of substance use with phenomena related to metacognition such as alexithymia (Saladin et al., 2012) and the ability to use metacognitive knowledge to respond to challenges (Lysaker et al., 2014). Chronic cannabis users have shown altered neural networks when completing a theory of mind task, similar to those at risk for the development of psychosis (Roser et al., 2012). It has also been suggested that persistent cannabis use results in difficulty determining and discriminating facial emotions (Bayrakçı et al., 2015).

2. Methods

2.1. Participants

Sixty-six participants (females = 3) with a diagnosis of schizophrenia ($n = 43$) or schizoaffective disorder ($n = 23$), as confirmed by the Structured Clinical Interview for DSM-IV (SCID-I) (Spitzer et al., 1995), were recruited from the Psychiatry Service of a VA Medical Center in Indianapolis, Indiana for a larger investigation on the effects of cognitive remediation on work outcome. Demographic information can be found in Table 1. During their participation, participants were being prescribed antipsychotic medication, receiving outpatient care and were stable as evidenced by no recent (1 month) hospitalizations, or changes in housing or medication. Participants with intellectual disability, defined as a chart diagnosis of mild mental retardation, or current substance dependence (including cannabis dependence, but excluding tobacco) were excluded.

2.2. Clinical assessments

Neurocognition was indexed via the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB), a commonly used index of cognition in schizophrenia (Nuechterlein et al., 2008). The MCCB assesses speed of processing, attention, working memory, verbal learning, visual

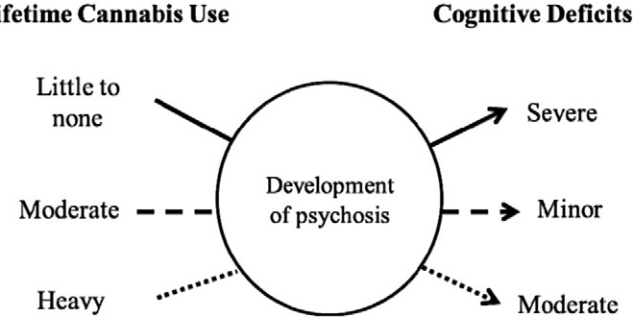

Fig. 1. Hypothetical paths to psychosis with lifetime cannabis use mediating cognitive impairment.

Table 1
Demographic information.

Demographic information			
Cluster:	1 (n = 34)	2 (n = 10)	3 (n = 22)
	Low cannabis/poor cognition	Heavy cannabis/moderately impaired cognition	Moderate cannabis/higher cognition
	Average (SD)	Average (SD)	Average (SD)
Age	52.53 (10.06)	51.60 (10.76)	45.82 (11.97)
Diagnosis (S/SA)	23/11	8/2	12/10
Gender (m/f)	33 (1)	10/0	20/2
Education (years)	12.29 (2.30)	12.30 (2.45)	13.55 (2.11)
IQ	89.75(15.25)	92.56 (14.08)	98.74 (13.52)
Race (AA/C/H)	14/20/0	4/6/0	10/11/1

Note: SD, standard deviation; S, schizophrenia; SA, schizoaffective disorder; m, male; f, female; IQ, intelligence; AA, African American; C, Caucasian; H, Hispanic.

learning, reasoning and problem solving, and social cognition. The total score of the seven domains was used as an overall index of neurocognitive capacity.

Metacognitive capacity was assessed with the Indiana Psychiatric Illness Interview (IPII) (Lysaker et al., 2002) and the Metacognitive Assessment Scale-Abbreviated (MAS-A) (Lysaker et al., 2005; Lysaker et al., 2014). The IPII is a semi-structured interview that asks subjects to discuss five domains, including (1) the story of their life, (2) if they believe themselves to have a mental illness, and if so, (3) how it may have affected their life, (4) how their illness controls their life, how they control their illness, as well as if their illness is affected by others and how much others have been affected by their illness, and (5) what they anticipate to remain the same or be different in the future with regard to their interpersonal and psychological experience. Unique from other psychiatric interviews the IPPI does not inquire about areas not spontaneously discussed, and thus it provides insight into synthetic metacognitive capacity. IPII responses were audio recorded, and transcribed for further assessment via the MAS-A.

The MAS-A assesses synthetic metacognition in four domains: self-reflectivity, awareness of the mind of the other, decentration, and mastery. The domain of self-reflectivity (S) represents an individual's ability to recognize one's own thoughts and emotions, how these influence one another, and/or how they change over time. Awareness of the mind of the other (O) represents an individual's capacity to recognize that others have their own thoughts and emotions. Decentration (D) reflects the ability to recognize that events occur of independent motive, outside of the individual. The domain of mastery (M) measures one's ability to cope with his/her mental illness. S and M domains are scored between 0 (least) and 9 (max), while O is scored between 0 (least) and 7 (max), and D on a 0 (least) to 3 (max) scale. Total MAS-A scores can range from 0 to 28, indicative of low to high metacognitive capacity, respectively.

Cannabis use was quantified through the Addiction Severity Index (ASI) (McLellan et al., 1980). The ASI asks participants to quantify the number of months they used cannabis at least three times a week. Symptoms of psychosis were assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The PANSS is a semi-structured interview, scored on a 30-item rating scale between 1 (absence of symptom) to 7 (extreme presence of symptom), and can be summed into a total score, as well as four subscores including positive, negative, hostile and cognitive symptoms. An intelligence quotient (IQ) was also derived with the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), which is a measure commonly used to assess IQ in both healthy individuals as well as those with schizophrenia spectrum disorder.

2.3. Procedures

Participants first underwent the informed consent process. Then, participant diagnoses were confirmed by the Structured Clinical Interview for the DSM-IV (Spitzer et al., 1995). Eligible participants were administered the MCCB, IPPI, ASI, and PANSS. After participation, each IPPI was transcribed and scored using the MAS-A. Raters on the PANSS and MAS-A were blind to subjects' cannabis use and neurocognitive performance.

2.4. Statistical analysis

A k-means cluster analysis was used to detect distinct group profiles based on lifetime cannabis use, neurocognitive ability, and metacognitive capacity. Unlike hierarchical cluster analyses, which use algorithms for the determination of cluster membership based on Euclidean distance measures, a k-means cluster analysis has been selected as this non-hierarchical technique forms clusters of limited within-cluster variation, compared to between cluster variation, to generate homogeneous groups (Mooi and Sarstedt, 2011; Norušis, 2012). Further, a k-means cluster analysis is most appropriate in the presence of existing hypotheses about the number of potential clusters within a sample (Norušis, 2012). Analysis consisted of four steps. Firstly, indexes of cannabis use (months), neurocognitive ability (MCCB total score) and metacognitive capacity (MAS-A) were normalized by converting scores into z-scores. Secondly, a k-means cluster analysis was performed to test the hypothesis that subjects could be differentiated into 3 groups based on little to no, moderate, and heavy lifetime cannabis use. Both 2 and 4 cluster formations were assessed to evaluate the validity of the 3 cluster model. Thirdly, final clusters were assessed for group differences in demographic characteristics including gender, diagnosis, age, education, and IQ via a multivariate general linear model. Fourthly, groups were assessed in the same manner for differences in symptom profiles as indexed by the total scores and subscores of the MCCB, MAS-A, and PANSS to better assess areas of each domain that may be suggestive of specific group differences. If groups differ in any demographic characteristic(s), these descriptors were used as co-variates in the multivariate general linear model to evaluate symptom, neurocognition and metacognitive profiles.

3. Results

The k-means cluster analysis indicated support for a 3-cluster solution (Fig. 2) based on uneven group membership in both 2- and 4-cluster model analyses. Clusters were labeled based on their clinical profiles: (1) low cannabis/poor cognition (n = 34); (2) heavy cannabis/moderately impaired cognition (n = 10); and (3) moderate cannabis/higher cognition (n = 22). A multivariate general linear model was then used to determine that the clusters were not significantly different ($p > .05$) on the basis of gender, diagnosis, age, education, or IQ. Because the groups failed to differ on demographic characteristics (Table 1), these factors were not included as covariates in further evaluation.

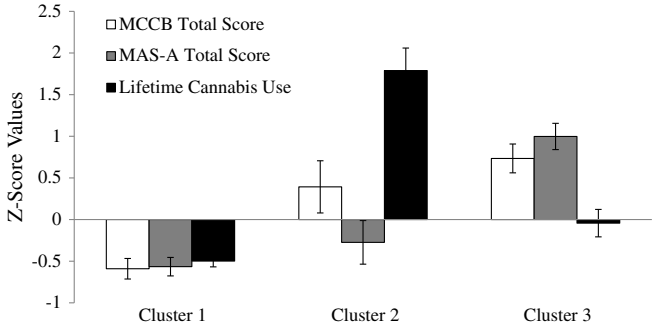

Fig. 2. Final clusters from k-means cluster analysis.

In the assessment of cluster differences, a multivariate general linear model with a factor of group (3: cluster 1, 2, or 3) yielded significant differences ($p < .05$) in domains of neurocognition, metacognition, and cannabis use, while demonstrating no group differences on the PANSS (Table 2). A one-way MANOVA revealed a significant multivariate main effect of group, Wilks' $\lambda = .052$, $F(46,82) = 6.059$, $p < .001$, partial eta squared =.773, and power to detect the effect was 1.000. Given the significance of the overall test, between-subject effects were evaluated for total score and subscores of the MCCB, MAS-A, and cannabis use.

Tests of between-subjects effects indicated significant differences on the MAS total score ($F(2,82) = 33.57$, $p < .001$), self-reflectivity ($F(2,82) = 21.00$, $p < .001$), other ($F(2,82) = 15.30$, $p < .001$), decentration ($F(2,82) = 12.81$, $p < .001$), and mastery ($F(2,82) = 21.16$, $p < .001$) (Fig. 3). Post hoc pairwise comparisons with Sidak correction for multiple comparisons yielded significant differences between Clusters 1 and 3 for MAS total score, as well as in subscores of self, other, decentration, and mastery ($p < .001$). Post hoc pairwise comparisons also yielded significant differences between clusters 2 and 3 for total score ($p < .001$), self ($p < .001$), other ($p = .005$), decentration ($p = .002$), and mastery ($p = .007$).

Tests of between-subject effects indicated significant differences for MCCB total ($F(2,82) = 20.01$, $p < .001$), speed ($F(2,82) = 10.56$, $p < .001$), attention ($F(2,82) = 7.16$, $p = .002$), working memory ($F(2,82) = 7.76$, $p = .001$), verbal ($F(2,82) = 5.58$, $p = .006$), visual ($F(2,82) = 5.50$, $p = .006$), reasoning ($F(2,82) = 3.95$, $p = .024$), and social cognition ($F(2,82) = 3.55$, $p = .034$). Post hoc pairwise comparisons with Sidak adjustments yielded significant differences between Clusters 1 and 3 for overall ($p < .001$), speed ($p < .001$), attention ($p = .001$), working memory ($p = .001$), verbal ($p = .009$), visual ($p = .028$), reasoning ($p = .030$), and social cognition ($p = .031$). Significant differences were observed between Clusters 1 and 2 for overall ($p = .003$) and visual ($p = .029$) scores. Additionally, Pearson's correlation revealed a significant, although small, correlation between the MAS-A total and MCCB overall scores for the group as a whole ($N = 66$) ($r = .243$, $p = .049$).

Significant differences between groups on lifetime cannabis use were observed ($F(2,82) = 52.09$, $p < .001$). Post hoc pairwise comparisons with Sidak adjustments demonstrated significant differences between Clusters 1 and 2 ($p < .001$), 1 and 3 ($p = .029$) and 2 and 3 ($p < .001$) (Fig. 4).

4. Discussion

The potential dose–response relationship between lifetime cannabis use and cognition was evaluated, as measured by neurocognitive

Table 2
Cluster profiles.

Cluster profiles				
Cluster:	1 ($n = 34$)	2 ($n = 10$)	3 ($n = 22$)	
	Low cannabis/poor cognition	Heavy cannabis/moderately impaired cognition	Moderate cannabis/higher cognition	Post hoc comparisons ($p < .05$)
	Average (SD)	Average (SD)	Average (SD)	
Metacognition (MAS-A)				
Total	9.07 (2.50)	10.20 (3.20)	15.11 (2.86)	1 < 3; 2 < 3
Self	3.68 (0.90)	3.90 (1.15)	5.68 (1.48)	1 < 3; 2 < 3
Other	2.43 (0.63)	2.60 (1.05)	3.52 (0.73)	1 < 3; 2 < 3
Decentration	0.33 (0.40)	0.30 (0.42)	0.93 (0.54)	1 < 3; 2 < 3
Mastery	2.66 (1.32)	3.40 (1.51)	4.98 (1.18)	1 < 3; 2 < 3
Cognition (MCCB)				
Total	19.56 (7.05)	29.20 (9.72)	32.55 (7.96)	1 < 3; 1 < 2
Speed	27.09 (9.66)	35.20 (10.04)	38.64 (8.88)	1 < 3
Attention	31.85 (9.23)	35.20 (7.70)	41.27 (9.44)	1 < 3
Working Memory	30.56 (9.76)	37.00 (11.05)	39.91 (6.03)	1 < 3
Verbal	32.65 (5.60)	37.90 (11.27)	38.32 (5.71)	1 < 3
Visual	29.68 (9.21)	39.20 (12.87)	36.95 (9.57)	1 < 3; 1 < 2
Reasoning	35.44 (5.19)	39.20 (6.58)	39.91 (7.30)	1 < 3
Social Cognition	32.35 (9.89)	37.00 (11.65)	40.55 (13.18)	1 < 3
Lifetime cannabis consumption (ASI)				
Mean	29.26 (64.93)	397.20 (137.57)	102.55 (124.24)	1 < 3; 1 < 2; 2 > 3
Median	.00[†]	432.0	30.00	
Symptom profile (PANSS)				
Positive	17.24 (5.58)	19.90 (3.90)	18.32 (4.05)	
Negative	19.71 (5.02)	22.40 (3.27)	18.36 (4.69)	
Cognitive	17.44 (4.05)	15.80 (3.05)	15.14 (3.01)	
Hostility	7.65 (3.63)	8.20 (2.90)	6.68 (2.36)	

Note: SD, standard deviation; MAS-A, Metacognitive Assessment Scale-Abbreviated; MCCB, MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB); ASI, Addiction Severity Index; PANSS, Positive and Negative Syndrome Scale (PANSS).
[†] Proportion of zeros was 64.7%.

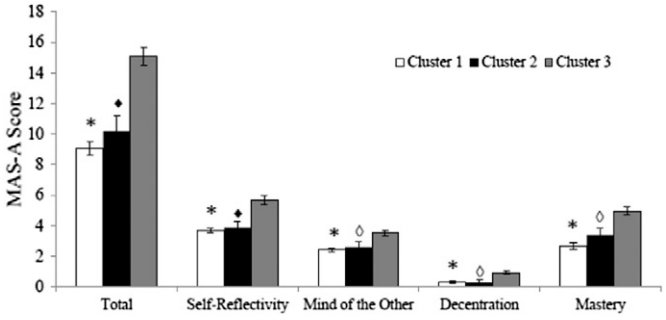

Fig. 3. Metacognitive profiles of clusters. * = 1 < 3, $p < .001$; ♦ = 2 < 3, $p < .001$; ◊ = 2 < 3, $p < .05$.

and metacognitive abilities, in schizophrenia spectrum disorder. Consistent with our hypotheses, increased lifetime cannabis use was associated with less impairment of neurocognition and metacognition compared to non-using peers; further, moderate cannabis use was associated with the least cognitive impairment compared to heavy users. The cluster analysis yielded three homogenous groups: (1) low cannabis/poor cognition; (2) heavy cannabis/moderately impaired cognition; and (3) moderate cannabis/higher cognition.

While this analysis was correlational and causality cannot be garnered, there are at least three plausible explanations for our findings. Firstly, data suggest that increased cannabis use may enhance cognition. Secondly, cannabis may be neuroprotective, thus individuals maintain cognitive capacity. These notions have been supported by preclinical (Peres et al., 2016; Zuardi et al., 2012) and human research (Leweke et al., 2012) investigating cannabidiol (CBD), a secondary chief constituent of cannabis, as an antipsychotic agent. Significantly, while these studies observed a decrease in positive symptoms of psychosis, evidence is lacking for CBD's effect on cognition. Additionally, if either explanation was true and a dose–response relationship existed, the highest use cannabis group would be expected to have the greatest cognitive ability. This relationship was not observed, however.

A third potential explanation for our findings generates from the complex relationship between cannabis use and psychotic experience. The association between cannabis and the development of psychosis has been observed in epidemiological research (Andréasson et al., 1987), meta-analyses (Henquet et al., 2005b; Moore et al., 2007), longitudinal research (Arendt et al., 2005; Niemi-Pynttäri et al., 2013), and direct Δ-9-THC administration studies (D'Souza et al., 2004; D'Souza et al., 2005; Morrison et al., 2009). Recently, Di Forti et al. (2015) have also indicated that cannabis, particularly of high Δ-9-THC content, uniquely contributed to approximately 24% of first episode psychosis cases in South London between 2005 to 2011, suggesting that cannabis is directly related to the development of new cases of schizophrenia. Therefore, it is plausible that at least a sub-set of individuals in our study with persistent cannabis use may have developed schizophrenia as a result of their cannabis use. Although speculative, this suggests that these individuals may have had higher premorbid neurocognitive and metacognitive capacity, compared to their non-using peers. Previous research supports this conclusion, finding that people with schizophrenia who reported cannabis use had higher premorbid IQ compared to non-using peers (Ferraro et al., 2013). This notion is also supported by the observation that both moderate and heavy cannabis use groups had significantly higher social cognition, supporting their ability to both procure and use cannabis initially, compared to the little to no cannabis use group. Additionally, the little to no cannabis use group showed significantly greater neurocognitive impairments compared to the moderate cannabis use group, in domains of speed, attention, working memory, verbal, visual, reasoning and social cognition. If cannabis use increased the vulnerability for the development of psychosis, it is also plausible that continued heavy use may lead to greater neurocognitive and metacognitive deficits, compared to moderate use. This speculative explanation is also supported by neurobiological underpinnings of cannabis use and its potential downstream effects on cognition (Volk and Lewis, 2016).

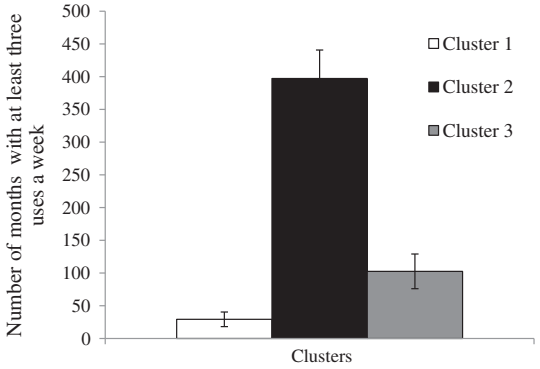

Fig. 4. Lifetime cannabis use of clusters. 1 < 3 < 2, $p < .05$.

In addition to these findings, our study also yielded the unexpected finding that the distinct groups failed to differ in severity of psychotic symptoms, suggesting that improved metacognitive ability may be independent from psychotic symptoms in cannabis-using individuals with psychosis. Additionally, moderate and heavy cannabis groups did not differ on neurocognitive ability. Greater group differences may not have been observed as a rare phenomenon unique to this sample, or due to the small cluster sizes. Alternatively, the lack of group differences may be due to a potentially more complex relationship between metacognition, symptoms of psychosis and cannabis use, in that when individuals are categorized based solely on metacognition groups demonstrate differences in observed symptomology (Hamm et al., 2012).

To the best of our knowledge, this was one of the first studies to characterize metacognitive ability in schizophrenia spectrum disorder with regard to cannabis use. The literature has found that individuals with schizophrenia spectrum disorder have impaired metacognitive capacity compared to healthy controls (Hasson-Ohayon et al., 2015; Ladegaard et al., 2014). Specifically, our findings suggested that individuals with low and heavy cannabis use were observed to have significantly poorer levels of metacognition. When we examined the MAS-A subscales to understand the clinical meaning of these deficits, we found that in regard to self-reflectivity both low and heavy cannabis use individuals demonstrated the ability distinguish between different cognitive operations and could name and partially distinguish valenced emotions. However, these groups were generally unable to see fallibility in their thinking. Moderate cannabis use individuals were able to recognize fallibility of their thoughts, and partially that their thoughts may not match what is possible in reality. However, moderate cannabis use individuals were unable to form

integrated depictions of themselves with understanding of how their thoughts and feelings were connected. Regarding the awareness of others' minds, both low and heavy cannabis use individuals were also able to recognize that others have autonomous mental activities, but were unable to distinguish different cognitive operations of others, as the moderate use group was able to do. Additionally, the moderate use group was also able to partially name and distinguish different emotions in others; however, these individuals were generally unable to discern others' intentions, and could not integrate thoughts, intentions and feelings of another. Regarding decentration, moderate cannabis users were also able recognize more often that they are not the center of others' mental activities, compared to both low and heavy cannabis using individuals who could not. Moderate users were, however, unable to acknowledge that others may perceive an event in a valid, although different way from their own. Finally, in regard to mastery, the moderate use group showed the highest level of mastery, demonstrating the ability to respond to their psychological problem by adjusting their behavior, although unable to change how they think about the problem. The low use group demonstrated occasional gross avoidance of their psychological problem, while the heavy use group was able to reach out for support, but showed only partial ability to change their behavior.

There are several limitations that should be addressed. The sample was largely male, with unbalanced and relatively small groups (e.g., $n = 10$ in cluster 2 of moderate users). Subjects with current substance dependence were also excluded. Replication is needed with a larger and broader sample, including women, individuals who are not currently undergoing treatment, and those actively meeting criteria for cannabis dependence. Also, the initiation of cannabis and psychotic symptoms are unknown. Importantly, it is also unclear if these neurocognitive and metacognitive profiles predate the onset of cannabis use, or are a result of use. The role of cognitive reserve was also not assessed, which will be important for future research. The results of this study may also not generalize to non-treatment seeking individuals, or those unwilling to participate in research. Finally, the content of the cannabis used by participants is also unknown.

Funding body agreements and policies

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Contributors

AMSM performed the literature review, completed the statistical analyses, and wrote the manuscript. PHL designed the study, wrote the protocol, and oversaw the completion of the analyses and writing of the manuscript. Authors AMSM, KAB, BJD, EAS, and KS assisted in scoring of clinical assessments. All authors contributed to and have approved the final version of the manuscript.

Conflict of interest

The authors have no conflict of interest to report.

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